

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

WHAT IS CLAIMED IS:

1                   1.       A method of controlling cancer suppression in a mammal having a  
2 cancer suppressing gene, comprising the steps of:  
3                   making a substantially duplicated genetic material corresponding to the  
4 genetic material of said gene, the substantially duplicated material selected from the group  
5 consisting of a cloned cancer suppressing gene, a modified or defective cancer suppressing  
6 gene, homologues thereof, fragments thereof, and mixtures thereof; and  
7                   interchanging said duplicated genetic material and the cancer suppressing gene  
8 of the mammal.

1                   2.       A method of claim 1, wherein before said making a substantially  
2 duplicated genetic material, determining the chromosomal location of said cancer suppressing  
3 gene of the mammal.

1                   3.       A method of claim 1, wherein after said making a substantially  
2 duplicated genetic material, detecting the presence or absence of an inactive cancer  
3 suppressing gene of a tissue sample of the mammal to determine whether or not the tissue  
4 sample cancer suppressing gene is defective or absent.

1                   4.       A method of claim 3, wherein in response to a determination that the  
2 tissue sample cancer suppressing gene is either defective or absent, replacing a cancer  
3 suppressing gene of the mammal with its clone.

1                   5.       A method of claim 3, wherein the determination of whether or not the  
2 tissue sample cancer suppressing gene is defective or absent is accomplished by measuring  
3 the amount of protein product of said cancer suppressing gene, of the tissue sample, bound by  
4 an antibody specific for said protein.

1                   6.       A method of claim 5, wherein the determination of whether or not the  
2 tissue sample cancer suppressing gene is defective or absent is accomplished by:

- 3                   (a)       labeling said tissue sample with radioactive isotope;
- 4                   (b)       lysing the labeled tissue;
- 5                   (c)       reacting the protein product of said cancer suppressing gene with an  
6 antibody specific for said protein thereby forming a protein/antibody immunocomplex;
- 7                   (d)       autoradiographing the immunocomplex obtained in step (c); and

8 (e) determining the presence or absence of the protein product by  
9 comparing the autoradiogram of step (d) with the autoradiogram of the standard protein  
10 product.

1 7. The method of claim 5, wherein the determination of whether or not  
2 the tissue sample cancer suppressing gene is defective or absent is accomplished by enzyme  
3 immunoassay techniques.

1 8. The method of claim 5, wherein the determination of whether or not  
2 the tissue sample cancer suppressing gene is defective or absent is accomplished by  
3 immunocytochemistry methods.

1 9. The method of claim 5, wherein the cancer suppressing gene is the RB  
2 gene and the protein product is ppRB<sup>110</sup>.

1 10. The method of claim 1, wherein said cancer suppressing gene is  
2 replaced with substantially duplicated material selected from the group consisting of said  
3 cloned cancer suppressing gene, homologues thereof, fragments thereof, and mixtures  
4 thereof, for therapeutic purposes.

1 11. The method of claim 1, wherein said cancer suppressing gene is  
2 replaced with substantially duplicated material selected from the group consisting of said  
3 defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures  
4 thereof, for facilitating the testing of the carcinogenicity of environmental influences.

1 12. The method of claim 2, wherein the location of said cancer suppressing  
2 gene is determined by chromosome walking.

1 13. The method of claim 2, wherein the location of said cancer suppressing  
2 gene is determined through organic markers.

1 14. A method of claim 2, wherein:  
2 said chromosomal location of said cancer suppressing gene is determined by  
3 testing genes of a chromosome for phenotypic expression;  
4 determining one of the genes of said chromosome to be a marker gene; and  
5 using chromosomal walking techniques to locate a cancer suppressing gene.

1           15.     An animal genetically altered so as to have the allele of at least one  
2 cancer suppressing gene selected from the group consisting of a defective allele, a homologue  
3 thereof, a fragment thereof, and a mixture thereof.

1           16.     An animal of claim 15, wherein said defective allele is selected from  
2 the group consisting of defective alleles of RB genes, breast cancer suppressing genes,  
3 Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes,  
4 bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes,  
5 small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes,  
6 acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homologues  
7 thereof, fragments thereof, and mixtures thereof.

1           17.     An animal of claim 15, wherein said allele contains a DNA fragment  
2 having at least one defective nucleotide sequence.

1           18.     An animal of claim 15, wherein said defective allele contains a DNA  
2 fragment having at least one defective RB nucleotide sequence.

1           19.     The animal of claim 15, wherein said animal is a mouse.

1           20.     A method for determining the carcinogenicity of suspected  
2 environmental influences, using the animal of claim 14, comprising the steps of:  
3                 exposing said animal to a suspected environmental influence;  
4                 observing the animal for the phenotypic expression of cancer; and  
5                 determining carcinogenicity of the suspected environmental influence in  
6 response to observing a phenotypic expression of cancer in the animal.

1           21.     A method of claim 20, wherein said exposing includes exposing to a  
2 source of radiation.

1           22.     A method of claim 20, wherein said exposing includes exposing to  
2 tobacco combustion products.

1           23.     A method of claim 20, wherein said exposing includes exposing to  
2 food additives.

1                   24.     A method of claim 20, wherein said exposing includes exposing to  
2     artificial substances.

1                   25.     A method of claim 20, wherein said observing includes examining the  
2     animal for tumor development.

1                   26.     A method of claim 25, wherein in response to the formation of a tumor  
2     in the animal, analyzing the tumor for the presence of cancer cells.

1                   27.     A method of making the animal of claim 15, comprising:  
2                   using at least one allele of an animal cancer suppressing gene selected from  
3     the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a  
4     mixture thereof;

5                   mutating at least one animal cell with said allele to form a mutated cell;  
6                   introducing said mutated cell into an animal blastocyst;  
7                   permitting growth of the blastocyst for a given period of time sufficient to  
8     incorporate said allele into its cells; repressing genetic recombinations within said cells;  
9     transferring the blastocyst containing said allele into the uterus of a pseudo pregnant animal  
10    for giving birth subsequently to an animal bearing said allele;

11                  breeding said animal to reproduce additional animals; and  
12                  selecting the animal of claim 14 from said additional animals by determining  
13    the presence therein of the said allele.

1                   28.     A method of claim 27, wherein before introducing said allele,  
2     removing said blastocyst from a super ovulated animal, and wherein said blastocyst is  
3     comprised of undifferentiated cells.

1                   29.     A method of claim 27, wherein said introducing is performed in vitro.

1                   30.     A pharmaceutical composition wherein the active ingredient is selected  
2     from the group consisting of a naturally occurring intact cancer suppressing gene, a cloned  
3     intact cancer suppressing gene, fragments thereof, homolgues thereof and mixtures thereof.

1                   31.     A pharmaceutical composition of claim 30, wherein said naturally  
2     occurring and cloned cancer suppressing gene is selected from the group consisting of RB  
3     genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-

Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homologues thereof, fragments thereof, and mixtures thereof.

32. A pharmaceutical composition of claim 30, wherein the active ingredient is selected from the group consisting of RB cDNA, modified RB cDNA fragment, clones thereof, homologues thereof and mixtures thereof.

33. A pharmaceutical composition of claim 31, wherein the active ingredient for each of said gene is selected from the group consisting of cDNA of said gene, fragments of said cDNA, homologues thereof and mixtures thereof.

34. A pharmaceutical composition of claim 32, wherein the cancer suppressing gene is isolated from human chromosome 13 region 13q14.

35. A pharmaceutical composition of claim 31, wherein the cancer suppressing gene and its clone each has the following nucleotide sequence:

TTCCGGTTTT	TCTCAGGGGA	CGTTGAAATT	ATTTTTGTAA	CGGGAGTCGG	GAGAGGACGG	60
GGCGTGCCCC	GCGTGCGCGC	GCGTCGTCTT	CCCCGGCGCT	CCTCCACAGC	TCGCTGGCTC	120
CCGCCGCGGA	AAGGCGTC	ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC	171			
		Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala				
		1 5 10				
ACC GCC GCC GCT GCC GCC GCG GAA CCC CCG GCA CCG CCG CCG CCG CCC	219					
Thr Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro Pro						
15 20 25						
CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG GAC CTG CCT	267					
Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro						
30 35 40						
CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA	315					
Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala						
45 50 55						
TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG	363					
Leu Cys Gln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp						
60 65 70 75						
TTA ACT TGG GAG AAA GTT TCA TCT GTG GAT GGA GTA TTG GGA GGT TAT	411					
Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr						
80 85 90						

33	ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA	459
34	Ile Gln Lys Lys Lys Glu Leu Trp Gly Ile Cys Ile Phe Ile Ala Ala	
35	95 100 105	
36		
37	GTT GAC CTA GAT GAG ATG TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC	507
38	Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn	
39	110 115 120	
40		
41	ATA GAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT	555
42	Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp	
43	125 130 135	
44		
45	ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT	603
46	Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr	
47	140 145 150 155	
48		
49	GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT	651
50	Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu	
51	160 165 170	
52		
53	ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT	699
54	Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser	
55	175 180 185	
56		
57	GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG	747
58	Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly	
59	190 195 200	
60		
61	GAA GTA TTA CAA ATG GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATG	795
62	Glu Val Leu Gln Met Glu Asp Leu Val Ile Ser Phe Gln Leu Met	
63	205 210 215	
64	CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC	843
65	Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu	
66	220 225 230 235	
67		
68	AAA GAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CGA	891
69	Lys Glu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg	
70	240 245 250	
71		
72	ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA	939
73	Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu	
74	255 260 265	
75		
76	GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT	987
77	Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys	
78	270 275 280	
79		
80	AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT	1035
81	Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe	
82	285 290 295	
83		
84	ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA	1083
85	Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu	
86	300 305 310 315	
87		
88	AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA	1131
89	Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu	
90	320 325 330	
91		
92	GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT	1179
93	Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser	

94					335					340					345				
95																			
96	ATA	GAC	AGT	TTT	GAA	ACA	CAG	AGA	ACA	CCA	CGA	AAA	AGT	AAC	CTT	GAT		1227	
97	Ile	Asp	Ser	Phe	Glu	Thr	Gln	Arg	Thr	Pro	Arg	Lys	Ser	Asn	Leu	Asp			
98					350						355				360				
99																			
100	GAA	GAG	GTG	AAT	GTA	ATT	CCT	CCA	CAC	ACT	CCA	GTT	AGG	ACT	GTT	ATG		1275	
101	Glu	Glu	Val	Asn	Val	Ile	Pro	Pro	His	Thr	Pro	Val	Arg	Thr	Val	Met			
102					365							370				375			
103																			
104	AAC	ACT	ATC	CAA	CAA	TTA	ATG	ATG	ATT	TTA	AAT	TCA	GCA	AGT	GAT	CAA		1323	
105	Asn	Thr	Ile	Gln	Gln	Leu	Met	Met	Ile	Leu	Asn	Ser	Ala	Ser	Asp	Gln			
106						380						390				395			
107																			
108	CCT	TCA	GAA	AAT	CTG	ATT	TCC	TAT	TTT	AAC	AAC	TGC	ACA	GTG	AAT	CCA		1371	
109	Pro	Ser	Glu	Asn	Leu	Ile	Ser	Tyr	Phe	Asn	Asn	Cys	Thr	Val	Asn	Pro			
110					400							405				410			
111																			
112	AAA	GAA	AGT	ATA	CTG	AAA	AGA	GTG	AAG	GAT	ATA	GGA	TAC	ATC	TTT	AAA		1419	
113	Lys	Glu	Ser	Ile	Leu	Lys	Arg	Val	Lys	Asp	Ile	Gly	Tyr	Ile	Phe	Lys			
114					415						420					425			
115																			
116	GAG	AAA	TTT	GCT	AAA	GCT	GTG	GGA	CAG	GGT	TGT	GTC	GAA	ATT	GGA	TCA		1467	
117	Glu	Lys	Phe	Ala	Lys	Ala	Val	Gly	Gln	Gly	Cys	Val	Glu	Ile	Gly	Ser			
118					430						435					440			
119																			
120	CAG	CGA	TAC	AAA	CTT	GGA	GTT	CGC	TTG	TAT	TAC	CGA	GTA	ATG	GAA	TCC		1515	
121	Gln	Arg	Tyr	Lys	Leu	Gly	Val	Arg	Leu	Tyr	Tyr	Arg	Val	Met	Glu	Ser			
122					445							450				455			
123																			
124	ATG	CTT	AAA	TCA	GAA	GAA	GAA	CGA	TTA	TCC	ATT	CAA	AAT	TTT	AGC	AAA		1563	
125	Met	Leu	Lys	Ser	Glu	Glu	Glu	Arg	Leu	Ser	Ile	Gln	Asn	Phe	Ser	Lys			
126					460						465					475			
127																			
128	CTT	CTG	AAT	GAC	AAC	ATT	TTT	CAT	ATG	TCT	TTA	TTG	GCG	TGC	GCT	CTT		1611	
129	Leu	Leu	Asn	Asp	Asn	Ile	Phe	His	Met	Ser	Leu	Leu	Ala	Cys	Ala	Leu			
130					480							485				490			
131																			
132	GAG	GTT	GTA	ATG	GCC	ACA	TAT	AGC	AGA	AGT	ACA	TCT	CAG	AAT	CTT	GAT		1659	
133	Glu	Val	Val	Met	Ala	Thr	Tyr	Ser	Arg	Ser	Thr	Ser	Gln	Asn	Leu	Asp			
134					495							500				505			
135																			
136	TCT	GGA	ACA	GAT	TTG	TCT	TTC	CCA	TGG	ATT	CTG	AAT	GTG	CTT	AAT	TTA		1707	
137	Ser	Gly	Thr	Asp	Leu	Ser	Phe	Pro	Trp	Ile	Leu	Asn	Val	Leu	Asn	Leu			
138					510						515					520			
139																			
140	AAA	GCC	TTT	GAT	TTT	TAC	AAA	GTG	ATC	GAA	AGT	TTT	ATC	AAA	GCA	GAA		1755	
141	Lys	Ala	Phe	Asp	Phe	Tyr	Lys	Val	Ile	Glu	Ser	Phe	Ile	Lys	Ala	Glu			
142					525							530				535			
143																			
144	GGC	AAC	TTG	ACA	AGA	GAA	ATG	ATA	AAA	CAT	TTA	GAA	CGA	TGT	GAA	CAT		1803	
145	Gly	Asn	Leu	Thr	Arg	Glu	Met	Ile	Lys	His	Leu	Glu	Arg	Cys	Glu	His			
146					540						545					550			
147																			
148	CGA	ATC	ATG	GAA	TCC	CTT	GCA	TGG	CTC	TCA	GAT	TCA	CCT	TTA	TTT	GAT		1851	
149	Arg	Ile	Met	Glu	Ser	Leu	Ala	Trp	Leu	Ser	Asp	Ser	Pro	Leu	Phe	Asp			
150					560							565				570			
151																			
152	CTT	ATT	AAA	CAA	TCA	AAG	GAC	CGA	GAA	GGA	CCA	ACT	GAT	CAC	CTT	GAA		1899	
153	Leu	Ile	Lys	Gln	Ser	Lys	Asp	Arg	Glu	Gly	Pro	Thr	Asp	His	Leu	Glu			
154					575						580					585			



— — —

```

216 AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG      2667
217 Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu
218      830      835      840
219
220 AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC      2715
221 Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu
222      845      850      855
223
224 AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA      2763
225 Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu
226      860      865      870      875
227
228 CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC      2811
229 Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu
230      880      885      890
231
232 CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT      2859
233 Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr
234      895      900      905
235
236 CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA      2907
237 Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser
238      910      915      920
239
240 AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT      2962
241 Asn Lys Glu Glu Lys
242      925
243
244 GGATTCATTG TCTCTCACAG ATGTGACTGT AT      2994

```

1                   36.     A pharmaceutical composition of claim 32, wherein said RB cDNA  
2 fragment is selected from the group consisting of RB-1, RB-2, RB-5, y79R8 and mixtures  
3 thereof.

1                   37.     A pharmaceutical composition of claim 32, wherein a resulting mRNA  
2 transcript of said RB cDNA fragment has 4.6 kb.

1                   38.     A pharmaceutical composition of claim 37, wherein the cloned  
2 genomic DNA has at least 27 exons.

1                   39.     A pharmaceutical composition of claim 30, wherein the cloned RB  
2 cDNA transcribes into mRNA which translates in protein having an amino acid sequence  
3 comprising:

4 MPPKTPRKTAATAAAAAAAEPPAPPPPPPEEDPE ( 34 )  
 5 QDSGPEDLPLVRLEFEETEEPDFTALCQKLKIPDHVRERA ( 74 )  
 6 WLTWEKVSSVDGVLGGYIQKKKELWGICIFIAAVDLDEMS (114)  
 7 FTFTELQKNIEISVHKFFNLLKEIDTSTKVDNAMSRLKK (154)  
 8 YDVLFAFSLKERTCELIYLTQPSSSISTEINSALVLKVS (194)  
 9 WITFLAKGEVLQMEDDLVISFQLNLCVLDYFIKLSPPML (234)  
 10 LKEPYKTAVIPINGSRPTPRRGQMRSARIAKQLENDTRII (274)  
 11 EVLCKEHECNIDEVKNVYFKNFIPFMNSLGLVTSNGLPEV (314)  
 12 ENLSKRYEEIYLKNKDLDDLARLFLDHDKTLQTDSDSFETQ (354)  
 13 RTPRKSNLDEEVNVIPTPTVMTNTIQQLMILNSASD (394)  
 14 QPSENLI SYFNCTVNPKE SILKRVKD IGYIFKEKFAKAV (434)  
 15 GQGCVEIGSQRYKLGVRLYYRVMESMLKSEEERLSIQNFS (474)  
 16 KLLNDNIFHMSLLACALEVVMATYSRSTSQNLD SGTDLSF (514)  
 17 PWILNVNLKAFDFYKVIESFIKAEGNLTREMIKHLERCE (554)  
 18 HRIMESLAWLSDSPLFDLIKQSKDREGPTDHLESACPLNL (594)  
 19 PLQNNHTAADMYLSPVRSPPKKKGSTTRVNSTANAETQATS (634)  
 20 AFQTQKPLKSTSLSLFYKKVYRLAYLRLNTLCERLLSEHP (674)  
 21 ELEHIIWTLFQHTLQNEYELMRDRHLDQIMMCSMYGICKV (714)  
 22 KNIDLKFKIIVTAYKDLPHAVQETFKRVLIKEEYDSIIV (754)  
 23 FYNSVFMQRLKTNILQYASTRPPTLSPIPHIPRSPYKFPS (794)  
 24 SPLRIPGGNIYISPLKSPYKISEGLPTPTKMTPRSRI LVS (834)  
 25 IGESFGTSEKFQKINQMV CNSDRVLKRS AEGSNPPKPLKK (874)  
 26 LRFDIEGSDEADGSKHLPGESKFQQKLAEMTSTRTRMQKQ (914)  
 27 KMND SMDTSNKEEK (928)  
 28  
 29

30 single-letter abbreviations for the amino acid residues are:  
 31 A, Ala; C, Cys; D, Asp; E, Gly; F, Phe; G, Gly; H, His;  
 32 I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln;  
 33 R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

1 40. A DNA nucleotide sequence comprising:  
 2  
 3 TTCCGGTTTT TCTCAGGGGA CGTTGAAATT ATTTTTGTAA CGGGAGTCGG GAGAGGACGG 60  
 4  
 5 GGCGTGCCCC GCGTGCGCGC GCGTCGTCCT CCCC GGCGCT CCTCCACAGC TCGCTGGCTC 120  
 6  
 7 CCGCCGCGGA AAGGCGTC ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC 171  
 8 Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala  
 9 1 5 10  
 10  
 11 ACC GCC GCC GCT GCC GCC GCG GAA CCC CCG GCA CCG CCG CCG CCG CCC 219  
 12 Thr Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro  
 13 15 20 25  
 14  
 15 CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG GAC CTG CCT 267  
 16 Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro  
 17 30 35 40  
 18  
 19 CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA 315  
 20 Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala  
 21 45 50 55  
 22  
 23 TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG 363

24	Leu	Cys	Gln	Lys	Leu	Lys	Ile	Pro	Asp	His	Val	Arg	Glu	Arg	Ala	Trp	
25	60					65					70					75	
26																	
27	TTA	ACT	TGG	GAG	AAA	GTT	TCA	TCT	GTG	GAT	GGA	GTA	TTG	GGA	GGT	TAT	411
28	Leu	Thr	Trp	Glu	Lys	Val	Ser	Ser	Val	Asp	Gly	Val	Leu	Gly	Gly	Tyr	
29					80					85					90		
30																	
31	ATT	CAA	AAG	AAA	AAG	GAA	CTG	TGG	GGA	ATC	TGT	ATC	TTT	ATT	GCA	GCA	459
32	Ile	Gln	Lys	Lys	Lys	Glu	Leu	Trp	Gly	Ile	Cys	Ile	Phe	Ile	Ala	Ala	
33				95					100					105			
34																	
35	GTT	GAC	CTA	GAT	GAG	ATG	TCG	TTC	ACT	TTT	ACT	GAG	CTA	CAG	AAA	AAC	507
36	Val	Asp	Leu	Asp	Glu	Met	Ser	Phe	Thr	Phe	Thr	Glu	Leu	Gln	Lys	Asn	
37			110					115					120				
38																	
39	ATA	GAA	ATC	AGT	GTC	CAT	AAA	TTC	TTT	AAC	TTA	CTA	AAA	GAA	ATT	GAT	555
40	Ile	Glu	Ile	Ser	Val	His	Lys	Phe	Phe	Asn	Leu	Leu	Lys	Glu	Ile	Asp	
41		125					130					135					
42																	
43	ACC	AGT	ACC	AAA	GTT	GAT	AAT	GCT	ATG	TCA	AGA	CTG	TTG	AAG	AAG	TAT	603
44	Thr	Ser	Thr	Lys	Val	Asp	Asn	Ala	Met	Ser	Arg	Leu	Leu	Lys	Lys	Tyr	
45	140					145					150					155	
46																	
47	GAT	GTA	TTG	TTT	GCA	CTC	TTC	AGC	AAA	TTG	GAA	AGG	ACA	TGT	GAA	CTT	651
48	Asp	Val	Leu	Phe	Ala	Leu	Phe	Ser	Lys	Leu	Glu	Arg	Thr	Cys	Glu	Leu	
49					160					165					170		
50																	
51	ATA	TAT	TTG	ACA	CAA	CCC	AGC	AGT	TCG	ATA	TCT	ACT	GAA	ATA	AAT	TCT	699
52	Ile	Tyr	Leu	Thr	Gln	Pro	Ser	Ser	Ser	Ile	Ser	Thr	Glu	Ile	Asn	Ser	
53				175					180					185			
54																	
55	GCA	TTG	GTG	CTA	AAA	GTT	TCT	TGG	ATC	ACA	TTT	TTA	TTA	GCT	AAA	GGG	747
56	Ala	Leu	Val	Leu	Lys	Val	Ser	Trp	Ile	Thr	Phe	Leu	Leu	Ala	Lys	Gly	
57			190					195				200					
58																	
59	GAA	GTA	TTA	CAA	ATG	GAA	GAT	GAT	CTG	GTG	ATT	TCA	TTT	CAG	TTA	ATG	795
60	Glu	Val	Leu	Gln	Met	Glu	Asp	Asp	Leu	Val	Ile	Ser	Phe	Gln	Leu	Met	
61		205					210				215						
62	CTA	TGT	GTC	CTT	GAC	TAT	TTT	ATT	AAA	CTC	TCA	CCT	CCC	ATG	TTG	CTC	843
63	Leu	Cys	Val	Leu	Asp	Tyr	Phe	Ile	Lys	Leu	Ser	Pro	Pro	Met	Leu	Leu	
64	220				225					230					235		
65																	
66	AAA	GAA	CCA	TAT	AAA	ACA	GCT	GTT	ATA	CCC	ATT	AAT	GGT	TCA	CCT	CGA	891
67	Lys	Glu	Pro	Tyr	Lys	Thr	Ala	Val	Ile	Pro	Ile	Asn	Gly	Ser	Pro	Arg	
68				240					245					250			
69																	
70	ACA	CCC	AGG	CGA	GGT	CAG	AAC	AGG	AGT	GCA	CGG	ATA	GCA	AAA	CAA	CTA	939
71	Thr	Pro	Arg	Arg	Gly	Gln	Asn	Arg	Ser	Ala	Arg	Ile	Ala	Lys	Gln	Leu	
72			255					260					265				
73																	
74	GAA	AAT	GAT	ACA	AGA	ATT	ATT	GAA	GTT	CTC	TGT	AAA	GAA	CAT	GAA	TGT	987
75	Glu	Asn	Asp	Thr	Arg	Ile	Ile	Glu	Val	Leu	Cys	Lys	Glu	His	Glu	Cys	
76			270					275				280					
77																	
78	AAT	ATA	GAT	GAG	GTG	AAA	AAT	GTT	TAT	TTC	AAA	AAT	TTT	ATA	CCT	TTT	1035
79	Asn	Ile	Asp	Glu	Val	Lys	Asn	Val	Tyr	Phe	Lys	Asn	Phe	Ile	Pro	Phe	
80		285				290					295						
81																	
82	ATG	AAT	TCT	CTT	GGA	CTT	GTA	ACA	TCT	AAT	GGA	CTT	CCA	GAG	GTT	GAA	1083
83	Met	Asn	Ser	Leu	Gly	Leu	Val	Thr	Ser	Asn	Gly	Leu	Pro	Glu	Val	Glu	
84	300				305					310					315		

85																			
86	AAT	CTT	TCT	AAA	CGA	TAC	GAA	GAA	ATT	TAT	CTT	AAA	AAT	AAA	GAT	CTA		1131	
87	Asn	Leu	Ser	Lys	Arg	Tyr	Glu	Glu	Ile	Tyr	Leu	Lys	Asn	Lys	Asp	Leu			
88					320					325					330				
89																			
90	GAT	GCA	AGA	TTA	TTT	TTG	GAT	CAT	GAT	AAA	ACT	CTT	CAG	ACT	GAT	TCT		1179	
91	Asp	Ala	Arg	Leu	Phe	Leu	Asp	His	Asp	Lys	Thr	Leu	Gln	Thr	Asp	Ser			
92				335					340					345					
93																			
94	ATA	GAC	AGT	TTT	GAA	ACA	CAG	AGA	ACA	CCA	CGA	AAA	AGT	AAC	CTT	GAT		1227	
95	Ile	Asp	Ser	Phe	Glu	Thr	Gln	Arg	Thr	Pro	Arg	Lys	Ser	Asn	Leu	Asp			
96			350					355					360						
97																			
98	GAA	GAG	GTG	AAT	GTA	ATT	CCT	CCA	CAC	ACT	CCA	GTT	AGG	ACT	GTT	ATG		1275	
99	Glu	Glu	Val	Asn	Val	Ile	Pro	Pro	His	Thr	Pro	Val	Arg	Thr	Val	Met			
100		365					370					375							
101																			
102	AAC	ACT	ATC	CAA	CAA	TTA	ATG	ATG	ATT	TTA	AAT	TCA	GCA	AGT	GAT	CAA		1323	
103	Asn	Thr	Ile	Gln	Gln	Leu	Met	Met	Ile	Leu	Asn	Ser	Ala	Ser	Asp	Gln			
104	380					385				390					395				
105																			
106	CCT	TCA	GAA	AAT	CTG	ATT	TCC	TAT	TTT	AAC	AAC	TGC	ACA	GTG	AAT	CCA		1371	
107	Pro	Ser	Glu	Asn	Leu	Ile	Ser	Tyr	Phe	Asn	Asn	Cys	Thr	Val	Asn	Pro			
108					400					405					410				
109																			
110	AAA	GAA	AGT	ATA	CTG	AAA	AGA	GTG	AAG	GAT	ATA	GGA	TAC	ATC	TTT	AAA		1419	
111	Lys	Glu	Ser	Ile	Leu	Lys	Arg	Val	Lys	Asp	Ile	Gly	Tyr	Ile	Phe	Lys			
112				415					420				425						
113																			
114	GAG	AAA	TTT	GCT	AAA	GCT	GTG	GGA	CAG	GGT	TGT	GTC	GAA	ATT	GGA	TCA		1467	
115	Glu	Lys	Phe	Ala	Lys	Ala	Val	Gly	Gln	Gly	Cys	Val	Glu	Ile	Gly	Ser			
116			430					435					440						
117																			
118	CAG	CGA	TAC	AAA	CTT	GGA	GTT	CGC	TTG	TAT	TAC	CGA	GTA	ATG	GAA	TCC		1515	
119	Gln	Arg	Tyr	Lys	Leu	Gly	Val	Arg	Leu	Tyr	Tyr	Arg	Val	Met	Glu	Ser			
120		445					450					455							
121																			
122	ATG	CTT	AAA	TCA	GAA	GAA	GAA	CGA	TTA	TCC	ATT	CAA	AAT	TTT	AGC	AAA		1563	
123	Met	Leu	Lys	Ser	Glu	Glu	Arg	Leu	Ser	Ile	Gln	Asn	Phe	Ser	Lys				
124	460				465					470				475					
125																			
126	CTT	CTG	AAT	GAC	AAC	ATT	TTT	CAT	ATG	TCT	TTA	TTG	GCG	TGC	GCT	CTT		1611	
127	Leu	Leu	Asn	Asp	Asn	Ile	Phe	His	Met	Ser	Leu	Leu	Ala	Cys	Ala	Leu			
128					480					485					490				
129																			
130	GAG	GTT	GTA	ATG	GCC	ACA	TAT	AGC	AGA	AGT	ACA	TCT	CAG	AAT	CTT	GAT		1659	
131	Glu	Val	Val	Met	Ala	Thr	Tyr	Ser	Arg	Ser	Thr	Ser	Gln	Asn	Leu	Asp			
132				495					500				505						
133																			
134	TCT	GGA	ACA	GAT	TTG	TCT	TTC	CCA	TGG	ATT	CTG	AAT	GTG	CTT	AAT	TTA		1707	
135	Ser	Gly	Thr	Asp	Leu	Ser	Phe	Pro	Trp	Ile	Leu	Asn	Val	Leu	Asn	Leu			
136			510					515					520						
137																			
138	AAA	GCC	TTT	GAT	TTT	TAC	AAA	GTG	ATC	GAA	AGT	TTT	ATC	AAA	GCA	GAA		1755	
139	Lys	Ala	Phe	Asp	Phe	Tyr	Lys	Val	Ile	Glu	Ser	Phe	Ile	Lys	Ala	Glu			
140		525					530					535							
141																			
142	GGC	AAC	TTG	ACA	AGA	GAA	ATG	ATA	AAA	CAT	TTA	GAA	CGA	TGT	GAA	CAT		1803	
143	Gly	Asn	Leu	Thr	Arg	Glu	Met	Ile	Lys	His	Leu	Glu	Arg	Cys	Glu	His			
144	540					545					550				555				
145																			

146	CGA	ATC	ATG	GAA	TCC	CTT	GCA	TGG	CTC	TCA	GAT	TCA	CCT	TTA	TTT	GAT	1851
147	Arg	Ile	Met	Glu	Ser	Leu	Ala	Trp	Leu	Ser	Asp	Ser	Pro	Leu	Phe	Asp	
148					560					565						570	
149																	
150	CTT	ATT	AAA	CAA	TCA	AAG	GAC	CGA	GAA	GGA	CCA	ACT	GAT	CAC	CTT	GAA	1899
151	Leu	Ile	Lys	Gln	Ser	Lys	Asp	Arg	Glu	Gly	Pro	Thr	Asp	His	Leu	Glu	
152				575					580					585			
153																	
154	TCT	GCT	TGT	CCT	CTT	AAT	CTT	CCT	CTC	CAG	AAT	AAT	CAC	ACT	GCA	GCA	1947
155	Ser	Ala	Cys	Pro	Leu	Asn	Leu	Pro	Leu	Gln	Asn	Asn	His	Thr	Ala	Ala	
156			590					595					600				
157																	
158	GAT	ATG	TAT	CTT	TCT	CCT	GTA	AGA	TCT	CCA	AAG	AAA	AAA	GGT	TCA	ACT	1995
159	Asp	Met	Tyr	Leu	Ser	Pro	Val	Arg	Ser	Pro	Lys	Lys	Lys	Gly	Ser	Thr	
160	605						610					615					
161																	
162	ACG	CGT	GTA	AAT	TCT	ACT	GCA	AAT	GCA	GAG	ACA	CAA	GCA	ACC	TCA	GCC	2043
163	Thr	Arg	Val	Asn	Ser	Thr	Ala	Asn	Ala	Glu	Thr	Gln	Ala	Thr	Ser	Ala	
164	620					625					630					635	
165																	
166	TTC	CAG	ACC	CAG	AAG	CCA	TTG	AAA	TCT	ACC	TCT	CTT	TCA	CTG	TTT	TAT	2091
167	Phe	Gln	Thr	Gln	Lys	Pro	Leu	Lys	Ser	Thr	Ser	Leu	Ser	Leu	Phe	Tyr	
168					640					645					650		
169																	
170	AAA	AAA	GTG	TAT	CGG	CTA	GCC	TAT	CTC	CGG	CTA	AAT	ACA	CTT	TGT	GAA	2139
171	Lys	Lys	Val	Tyr	Arg	Leu	Ala	Tyr	Leu	Arg	Leu	Asn	Thr	Leu	Cys	Glu	
172				655					660					665			
173																	
174	CGC	CTT	CTG	TCT	GAG	CAC	CCA	GAA	TTA	GAA	CAT	ATC	ATC	TGG	ACC	CTT	2187
175	Arg	Leu	Leu	Ser	Glu	His	Pro	Glu	Leu	Glu	His	Ile	Ile	Trp	Thr	Leu	
176			670					675					680				
177																	
178	TTC	CAG	CAC	ACC	CTG	CAG	AAT	GAG	TAT	GAA	CTC	ATG	AGA	GAC	AGG	CAT	2235
179	Phe	Gln	His	Thr	Leu	Gln	Asn	Glu	Tyr	Glu	Leu	Met	Arg	Asp	Arg	His	
180	685						690					695					
181																	
182	TTG	GAC	CAA	ATT	ATG	ATG	TGT	TCC	ATG	TAT	GGC	ATA	TGC	AAA	GTG	AAG	2283
183	Leu	Asp	Gln	Ile	Met	Met	Cys	Ser	Met	Tyr	Gly	Ile	Cys	Lys	Val	Lys	
184	700					705					710				715		
185																	
186	AAT	ATA	GAC	CTT	AAA	TTC	AAA	ATC	ATT	GTA	ACA	GCA	TAC	AAG	GAT	CTT	2331
187	Asn	Ile	Asp	Leu	Lys	Phe	Lys	Ile	Ile	Val	Thr	Ala	Tyr	Lys	Asp	Leu	
188					720					725					730		
189																	
190	CCT	CAT	GCT	GTT	CAG	GAG	ACA	TTC	AAA	CGT	GTT	TTG	ATC	AAA	GAA	GAG	2379
191	Pro	His	Ala	Val	Gln	Glu	Thr	Phe	Lys	Arg	Val	Leu	Ile	Lys	Glu	Glu	
192				735					740					745			
193																	
194	GAG	TAT	GAT	TCT	ATT	ATA	GTA	TTC	TAT	AAC	TCG	GTC	TTC	ATG	CAG	AGA	2427
195	Glu	Tyr	Asp	Ser	Ile	Ile	Val	Phe	Tyr	Asn	Ser	Val	Phe	Met	Gln	Arg	
196			750					755					760				
197																	
198	CTG	AAA	ACA	AAT	ATT	TTG	CAG	TAT	GCT	TCC	ACC	AGG	CCC	CCT	ACC	TTG	2475
199	Leu	Lys	Thr	Asn	Ile	Leu	Gln	Tyr	Ala	Ser	Thr	Arg	Pro	Pro	Thr	Leu	
200			765				770					775					
201																	
202	TCA	CCA	ATA	CCT	CAC	ATT	CCT	CGA	AGC	CCT	TAC	AAG	TTT	CCT	AGT	TCA	2523
203	Ser	Pro	Ile	Pro	His	Ile	Pro	Arg	Ser	Pro	Tyr	Lys	Phe	Pro	Ser	Ser	
204	780					785						790				795	
205																	
206	CCC	TTA	CGG	ATT	CCT	GGA	GGG	AAC	ATC	TAT	ATT	TCA	CCC	CTG	AAG	AGT	2571

207 Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser  
 208 800 805 810  
 209  
 210 CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA 2619  
 211 Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro  
 212 815 820 825  
 213  
 214 AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG 2667  
 215 Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu  
 216 830 835 840  
 217  
 218 AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC 2715  
 219 Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu  
 220 845 850 855  
 221  
 222 AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA 2763  
 223 Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu  
 224 860 865 870 875  
 225  
 226 CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC 2811  
 227 Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu  
 228 880 885 890  
 229  
 230 CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT 2859  
 231 Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr  
 232 895 900 905  
 233  
 234 CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA 2907  
 235 Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser  
 236 910 915 920  
 237  
 238 AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT 2962  
 239 Asn Lys Glu Glu Lys  
 240 925  
 241  
 242 GGATTCATTG TCTCTCACAG ATGTGACTGT AT 2994

1 41. A method of therapeutically treating inactive, mutative or absent  
 2 cancer suppressing genes comprising:  
 3 treating said inactive, mutative or absent cancer suppressing genes with at  
 4 least a portion of intact cancer suppressing genes.

1 42. A method of claim 41, wherein said cancer suppressing genes are each  
 2 a substance selected from the groups consisting of RB genes, breast cancer suppressing  
 3 genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes,  
 4 bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes,  
 5 small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes,  
 6 acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, and mixtures  
 7 thereof.

1 43. A method of claim 41, wherein said treating includes:

2           treating said inactive, mutative or absent cancer suppressing gene with a  
3 substance selected from the group consisting of an RB gene, a portion of said gene, or a  
4 mixture thereof.

1           44.     A method of claim 43, wherein said portion is selected from the group  
2 consisting of RB cDNA, RB cDNA fragment, homologues thereof and mixtures thereof.

1           45.     The method of claim 41, wherein the intact cancer suppressing gene, or  
2 portion thereof, is delivered to the site of a tumor by means of a retrovirus.

1           46.     A method of claim 41, wherein the intact cancer suppressing gene, or a  
2 portion thereof, is delivered to the site of a tumor by a liposome.

1           47.     A method of claim 41, wherein the location of said cancer suppressing  
2 gene is determined by utilizing a genetic marker.